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GLOBAL PATENT GROUP - KAL
1005 North Warson Road
Suite 201
St. Louis, MO 63132

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RAO, DEEPAK R	

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEVIN LIU and CUNXIANG ZHAO

Appeal 2009-015302
Application 10/820,647
Technology Center 1600

Before TONI R. SCHEINER, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-13, 18-36, 41-49, 51-57, and 59-69, directed to a pharmaceutical compound and methods of using it. The claims have been rejected as lacking enablement. We have jurisdiction under 35 U.S.C. § 6(b).

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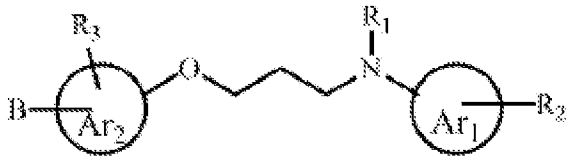
[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

"[T]he present invention relates to aryl compounds and methods for treating various diseases by modulation of nuclear receptor mediated processes . . . in particular processes mediated by peroxisome proliferator activated receptors (PPARs)" (Spec. 1).

Representative claim 1 is directed to an aryl compound having the structure of Formula I:

(I) 

wherein [Ar_1, Ar_2, R_1, R_2, R_3, B, and R_4 are as detailed on page 25 of Appellant's Brief on Appeal, in the Claims Appendix],

"or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof."

Representative claim 51 reads: "A method of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting said PPAR with a compound of Claim 1 and monitoring a change in cell phenotype, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner."

Representative claim 59 reads: "A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient."

Finally, representative claim 60 reads: "A method of treating a metabolic disorder or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient."

The Examiner rejected the claims as follows:[2]

(A) Claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 under the first paragraph of 35 U.S.C. § 112 "because the specification, while being enabling for a compound of Formula I or a pharmaceutically acceptable N-oxide or salt thereof, does not reasonably provide enablement for a pharmaceutically acceptable prodrug, metabolite, ester, amide or solvate thereof" (Ans. 4); and

(B) claims 51-57 and 59-65 under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for a method for treatment of diabetes, does not reasonably provide enablement" for the various methods recited in these claims (*id.* at 10).

We reverse.

ENABLEMENT REJECTION A

Findings of Fact

1. The Examiner rejected claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 "because the specification, while being enabling for a compound of Formula I or . . . [an] N-oxide or salt thereof does not reasonably provide enablement for a pharmaceutically acceptable prodrug, metabolite, ester, amide or solvate thereof" (Ans. 4).

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[2] Claims 50 and 70 have been allowed (Final Rej., October 4, 2007). Claims 14-16, 37-40, and 58 have been cancelled (App. Br. 3).

2. The Specification teaches that an amide is "a chemical moiety with formula -C(O)NHR or -NHC(O)R, where R is optionally substituted" and "[a]ny amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be amidified" (Spec. 13).

3. "The procedures and specific groups to be used to . . . make[ ] such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., . . . 1999, which is incorporated herein by reference" (Spec. 13).

4. The Specification defines a prodrug as "an agent that is converted into the parent drug *in vivo*" (Spec. 27).

> An example . . . would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

(*Id.*)

5. The Specification teaches that "the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like" (Spec. 19).

6. West,[3] a reference cited by the Examiner, teaches that

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[3] ANTHONY R. WEST, SOLID STATE CHEMISTRY AND ITS APPLICATIONS 358, 365 (1988).

> The factors that govern whether or not solid solutions [i.e., hydrates and solvates], especially the more complex ones, form are understood only qualitatively. For a given system, it is not usually possible to predict whether solid 'solutions' will form or, if they do form, what is their compositional extent. Instead, this has to be determined experimentally.

(West 365.)

7. Vippagunta,[4] another reference cited by the Examiner, teaches:

> Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates.

(Vippagunta 18.)

Discussion

The Examiner acknowledges that "[t]he term 'prodrug' [is] generally known to represent 'a physiologically functional derivative, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the invention or an active metabolite thereof'" (Ans. 4-5). In addition, the Examiner acknowledges

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[4] Sudha R. Vippagunta et al., *Crystalline solids*, 48 ADVANCED DRUG DELIVERY REVIEWS 3-26 (2001).

that "many strategies for making prodrugs" were known in the art at the time of the invention (*id.* at 6).

However, the Examiner concludes that the Specification is not enabling for prodrugs or pharmaceutically active metabolites of the compound of Formula I because "[t]he term 'prodrug and/or 'metabolite' is directed to esters and amides of compounds of Formula I" (*id.* at 5), but the "substituent groups in Formula I already include . . . acids, esters, amides, etc." (*id.*), and "[t]he specification does not provide what other 'compounds' . . . are intended to be the above refer[enc]ed 'prodrugs' and 'metabolites'" (*id.*). In other words, because the Specification doesn't provide examples of other amide or ester derivatives of the compound of Formula I capable of functioning as prodrugs or pharmaceutically active metabolites, the Examiner concludes "[i]n a clinical trial setting, it would require undue experimentation to determine whether a particular compound meets the criteria of a 'prodrug'" or metabolite (*id.* at 6).

In addition, the Examiner concludes that "[t]he quantity of experimentation needed [to make solvates of the compound of Formula I] would be an undue burden on [one] skilled in the chemical art" (*id.* at 10) because "[t]he state of the art is that [it] is not predictable whether solvates will form or what their composition will be" (*id.* at 7). The Examiner notes that "some of the exemplified compounds within the claimed genus were in contact with solvent . . . [but] have not formed solvate" (*id.* at 6), thus, "[t]here is no evidence that solvates of these compounds actually exist" (*id.* at 9).

Nevertheless,

> [T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by . . . [a] claim is not adequately enabled by the description of the invention provided in the specification . . . this includes . . . providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.

In re Wright, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993).

In other words, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." *In re Armbruster*, 512 F.2d 676, 678 (CCPA 1975). Instead, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

Thus, the threshold issue raised by this rejection is not whether Appellants have established that their Specification is enabling for making prodrugs, pharmaceutically active metabolites, esters, amides or solvates of the compound of Formula I. Rather, the issue is whether the Examiner has met his initial burden of providing a reasonable explanation as to why it isn't.

The Examiner's explanation as to why it would have required undue experimentation for one skilled in the art to make and/or use prodrugs, metabolites, esters, amides or solvates of the compound of Formula I is insufficient to satisfy that initial burden.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art . . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Forman, 230 USPQ 546, 547 (BPAI 1986). "The key word is 'undue,' not 'experimentation.'" *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).

Essentially, we agree with Appellants that the Examiner has overemphasized the importance of working examples (App. Br. 10), and given "too little credit to the abilities of a person having ordinary skill in the art" (*id.* at 11).

Even accepting that the experimentation required to produce prodrugs and metabolites based on the compound of Formula I would be tedious and time-consuming, the Examiner has not established that it would have been anything other than routine and empirical for one of skill in the art.

In addition, while the West and Vippagunta references show that it is difficult to predict whether a given compound will form a solvate or hydrate, or what its composition will be, the references also provide evidence that solvates and hydrates are routinely produced and characterized empirically (FF 6, 7). As for the Examiner's concern that some of the compounds of the invention were in contact with solvents, but didn't form solvates (Ans. 6), Appellants point out that the examples in the Specification used "a drying agent . . . to remove trace amounts of water as part of the purification

process following a number of the chemical steps involved in the syntheses of exemplary compounds" (App. Br. 14), thus, "conditions . . . were unfavorable for solvate formation and therefore not indicative of the nonexistence of solvates" (*id.* at 14-15).

Conclusion

The Examiner has failed to provide a reasonable explanation as to why pharmaceutically acceptable prodrugs, metabolites, esters, amides or solvates of Formula I are not adequately enabled by the description of the invention provided in the Specification.

ENABLEMENT REJECTION B

Findings of Fact

8. The Examiner concedes that the Specification is enabling for a method of treating diabetes, but maintains the rejection of claims 51-57 and 59-65 because

> [T]he specification . . . does not reasonably provide enablement for a method of modulating a peroxisome proliferator[]-activated receptor (PPAR) function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a disease generally; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally.

(Ans. 10.)

9. According to the Specification:

> Biological processes modulated by PPAR . . . include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinemia . . . , macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte formation.

(Spec. 1-2.)

10. The Specification teaches that "[s]ubtypes of PPAR include PPAR-alpha, PPAR-delta (also known as . . . PPAR-beta . . .) and two isoforms of PPAR-gamma" (Spec. 2). All of the isoforms "have been shown to be important molecular targets for treatment of metabolic and other diseases" (*id.* at 3), and "[c]ompounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models" (*id.* at 1).

11. According to the Specification, activators of PPAR-gamma "have been clinically shown to enhance insulin-action, to reduce serum glucose and to have small but significant effects on reducing serum triglyceride levels in patients with Type 2 diabetes" (Spec. 2); and "have been implicated in the treatment of polycystic ovary syndrome" (*id.* at 24).

12. "Pharmacological PPAR-alpha activators . . . are used particularly for the treatment of hypertriglyceridemia, hyperlipidemia and obesity" and "may be useful in treating atherosclerotic diseases" (Spec. 24-25).

13. "PPAR-delta . . . has been shown to be a valuable molecular target for treatment of dyslipedimia [sic] and other diseases" (Spec. 2).

14. The Specification teaches that

> [T]he disease to be treated by the methods of the present invention is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

(Spec. 25.)

15. According to the Specification:

> The term "modulate" refers to the ability of a compound of the invention to alter the function of a PPAR. A modulator may activate the activity of a PPAR, may activate or inhibit the activity of a PPAR depending on the concentration of the compound exposed to the PPAR, or may inhibit the activity of a PPAR. The term "modulate" also refers to altering the function of a PPAR by increasing or decreasing the probability that a complex forms between a PPAR and a natural binding partner.

(Spec. 20-21.)

16. The Specification teaches that "[c]ompounds may be screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR [α, γ, and δ] subtypes" (Spec. 22). Eighteen "compounds were evaluated in a cell-based [transfection] assay to determine their human PPAR [α, γ, and δ] activity" (Spec. 48). The results, displayed in the Table on pages 49-51 of the Specification, show that most of the compounds tested were able to activate two or more PPAR subtypes under experimental conditions, while a few compounds were unable to activate any subtype at all.

17. Fayer,[5] a reference cited by the Examiner, teaches that there is a "[l]ack of correlation between in vitro inhibition of CYP3A-mediated metabolism by [RG 12525] a PPAR-gamma agonist and its effect on the clinical pharmacokinetics of midazolam, an in vivo probe of CYP3A

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[5] JL Fayer et al., *Lack of correlation between in vitro inhibition of CYP3A-mediated metabolism by a PPAR-gamma agonist and its effect on the clinical pharmacokinetics of midazolam, an in vivo probe of CYP3A activity*, 41 J. CLIN. PHARMACOL. 305-316 (2001) (Abstract only).

activity," probably due to "the high degree of RG 12525 protein binding" (Fayer, Abstract). Fayer emphasizes "the need to recognize factors other than plasma drug concentrations and potency of in vitro enzyme inhibition when extrapolating in vitro data to predict in vivo drug-drug interactions" (*id.*).

Discussion

The threshold issue raised by this rejection is whether the Examiner has met his initial burden of providing a reasonable explanation as to why the Specification isn't enabling for using the compounds of Formula I to modulate a PPAR function, treat a PPAR-modulated disease or condition, inhibit the formation of adipocytes, treat a metabolic disorder, or treat a variety of specifically identified diseases.

With respect to claims 51 and 52, directed to "modulating a PPAR function," the Examiner argues that modulating "generally encompasses blocking, activating, partial blocking and partial activating. However, the compounds were not shown to have all these properties . . . [and] it is revolutionary for a compound to be effective as a blocker, activator and partial blocker/activator" (Ans. 11).

However, the Examiner's interpretation of the term "modulating" doesn't comport with the Specification's definition of the term (FF15). We agree with Appellants that "nowhere in the specification is it suggested that any of the claimed compounds have the ability to block, activate partially block and partially activate a PPAR function at the same time" (App. Br. 18).

With respect to the remaining claims, the Examiner finds that "one having ordinary skill in the art would have to undergo an undue amount of

experimentation to use the claimed compounds as PPAR regulators" (Ans. 11), because PPAR activity "is highly structure specific and unpredictable as can be seen from the range of the results obtained for the tested compounds" (*id.* at 10-11).

However, the "range of results" obtained for the 18 compounds tested simply reflects the fact that most of the compounds were able to activate two or more PPAR subtypes, while a few were unable to activate any subtype at all (FF16). The Specification teaches, and the Examiner does not dispute, that all of the isoforms "have been shown to be important molecular targets for treatment of metabolic and other diseases" (Spec. 3; FF10) - so it's not clear why structure specificity would be a problem, especially as the Specification discloses an assay for determining subtype specificity.

The Examiner also argues that "there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR" (Ans. 11). The Examiner cites Fayer as evidence that "such correlation or lack thereof is important to predict drug-drug interactions" (*id.*), but doesn't elaborate further.

Again, it is the Examiner's initial burden to "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Marzocchi*, 439 F.2d at 224. The Examiner has not done so.

Finally, the Examiner acknowledges that the Specification "provides a select list of disorders such as diabetes, hyperinsulinemia, atherosclerosis, etc." (Ans. 12) to be treated with the compounds of Formula I, but argues

that "[c]laims are drawn to a method for treatment of 'a PPAR-modulated disease or condition' . . . include[ ] disorders that are known to exist and those that may be discovered in the future and therefore, [are] extremely broad" (*id.*).

Nevertheless, it is well settled that the purpose of the Specification is not to "enable technology that arises after the date of application. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004).

Conclusions

The Examiner has failed to meet the initial burden of providing a reasonable explanation as to why the Specification isn't enabling for using the compounds of Formula I to modulate a PPAR function, treat a PPAR-modulated disease or condition, inhibit the formation of adipocytes, treat a metabolic disorder, or treat a variety of specifically identified diseases.

SUMMARY

(A) The rejection of claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 under the enablement provision of 35 U.S.C. § 112, first paragraph, is reversed.

(B) The rejection of claims 51-57 and 59-65 under the enablement provision of 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

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GLOBAL PATENT GROUP - KAL
1005 NORTH WARSON ROAD
SUITE 201
ST. LOUIS, MO 63132